DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Division of Biostatistics and Epidemiology (HFM-215)

Memorandum

BLA NUMBER: *97-1359*

SPONSOR: *MedImmune, Inc.*

DATE: April 3, 1998

FROM: *Teresa Neeman, Ph.D.*

THROUGH: *Peter A. Lachenbruch, Ph.D., Chief, Biostatistics Branch*

SUBJECT: *Statistical Review, MEDI-493 (Palivizumab) Humanized Monoclonal Antibody to RSV F Protein*

TO: *Dr. Dwaine Rieves, Clinical Reviewer*
Division of Clinical Trial Design and Analysis (DCTDA) HFM-576

CC: *original/DCC/HFM-99*
Dr. S. Ellenberg/HFM-210
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BACKGROUND

The proposed indication for MEDI-493 (Palivizumab) is for the prophylaxis of severe respiratory syncytial virus (RSV) in premature infants or infants with bronchopulmonary dysplasia (BPD). Support for this application comes primarily from a single randomized, double-blind, placebo-controlled multicenter study (MI-CP018) in 1502 premature infants or infants with BPD randomized in a 2:1 ratio to receive multiple doses of MEDI-493 or placebo. This clinical trial enrolled patients between November 15, 1996 and December 13, 1996 at 139 investigative sites in the northern hemisphere: 99 sites in the U.S., 9 sites in Canada and 11 sites in the UK. Patients were to be followed for 5 months, over a time period which covered the winter season when these children are at highest risk for RSV. The primary endpoint of this study was the incidence of RSV hospitalization. Other endpoints included the number of RSV hospitalization days, the number of RSV hospitalization days requiring supplemental oxygen, the days of RSV

hospitalization with moderate to severe lower respiratory tract infection, the incidence and number of ICU days, and the incidence and number of mechanical ventilation days. Additional secondary endpoints included incidence of all hospitalizations and incidence of otitis media (see protocol/statistical plan, vol. 46, pp. 3-4).

PATIENT DISPOSITION

According to the study report, approximately 99% of the enrolled patients completed the study. A patient was considered to be a noncompleter on study if he/she was not followed for 150 days and did not have a documented RSV hospitalization. Of the patients who failed to complete the study (5/500 or 1% on placebo, and 11/1002 or 1% on MED-493), seven patients died, four withdrew consent and five were lost to follow-up. A summary of these data appear in the table below:

	Placebo	MEDI-493
number of patients enrolled	500	1002
# of patients not completing		
death	*5*	*2*
withdrew consent	*0*	*4*
lost to follow-up	*0*	*5*
# of patients completing study	495 (99%)	991 (99%)

Demographic and Other Baseline Characteristics

The statistical reviewer verified the demographic characteristics of the two randomized groups using the SAS data set provided by the sponsor. This summary is presented on the table below and is consistent with the summary tables presented by the sponsor.

		Placebo (N=500)	MEDI-493 (N=1002)	total (N=1502)
Age at study entry (months)	median	4.6 months	4.3 months	4.4 months
	(Q1,Q3)	(2.6 , 7.3)	(2.6, 6.7)	(2.6, 6.9)
	range	0.2-23.9	0.07-24.0	0.07-24.0
Gestational Age (weeks)	median	29 weeks	29 weeks	29 weeks
	(Q1-Q3)	(26, 32)	(27, 32)	(27, 32)
	range	22-41	22-40	22-41
Weight at study entry (kg)	median	4.6 kg	4.5 kg	4.5 kg
	(Q1-Q3)	(3.2, 6.3)	(3.1, 6.0)	(3.1, 6.2)
	range	1.4-13.6	1.1-14.2	1.1-14.2
	missing	3 NA	4 NA	7 NA
Gender				
	male	284 (57%)	570 (57%)	854 (57%)
	female	216 (43%)	432 (43%)	648 (43%)
Race				
	Caucasian	287 (57%)	585 (58%)	872 (58%)
	Black	128 (26%)	228 (23%)	356 (24%)
	Hispanic	54 (11%)	110 (11%)	164 (11%)
	Asian	12 (2%)	21 (2%)	33 (2%)
	Other	19 (4%)	58 (6%)	77 (5%)

ANALYSIS OF PRIMARY ENDPOINT/ SPONSOR

The sponsor tabulated the number of patients with documented RSV hospitalizations in each group and tested the hypothesis of no association between treatment and outcome using a two-sided Fisher's Exact Test. In accordance with their prospectively defined primary analysis, noncompleters were counted as having no RSV hospitalization. A summary of these data, together with the p-value, were verified by the reviewing statistician and appear in the table below.

	Placebo (N=500)	MEDI-493 (N=1002)	total (N=1502)
RSV hospitalization	53 (11%)	48 (5%)	101 (7%)
no RSV hospitalization	447 (89%)	954 (95%)	1401 (93%)
Fisher's Exact Test $p < 0.0001$			

PRIMARY ENDPOINT ANALYSIS/ FDA

Deaths Included in the Primary Endpoint: There were 4 (.4%) deaths in the treatment arm and 5 deaths (2.5%) in the control arm. Two of the infants in the treatment arm died following an RSV hospitalization, but the other seven deaths were counted among those not experiencing an RSV hospitalization. If those seven patients are also counted as treatment failures (i.e. RSV hospitalization, the evidence of treatment efficacy becomes even stronger. A summary of the data for the combined endpoint, RSV hospitalization or death, is presented in the table below:

combined endpoint	**Placebo (N=500)**	**MEDI-493 (N=1002)**	**total (N=1502)**
RSV hospitalization or death	58 (12%)	50 (5%)	101 (7%)
neither RSV hospitalization nor death	442 (88%)	952 (95%)	1401 (93%)
Fisher's Exact Test $p < 0.0001$			

Vaccine Efficacy: In vaccine trials, the estimate of efficacy, called vaccine efficacy (VE), can be expressed as a function of the relative risk (RR). Specifically, it is defined as a percent by the formula:

$$VE\,(\%) = 100 * (1 - \frac{P(\,RSV\ hospitatization|\ MEDI-493)}{P(\,RSV\ hospitalization\,|\,Placebo)}) = 100 * (1 - RR),$$

when exposure time is the same for all patients. The point estimate in this trial for vaccine efficacy was 58%, with a 95% confidence interval (computed using StatXact) of (34%, 69%).

Primary Efficacy Endpoint/ by Country: Over 85% of the infants enrolled came from sites in the United States, and the overall results are largely driven by what happened in these centers. However, results from Canada and the U.K. showed a very similar pattern of a reduction in RSV hospitalization. A summary of these data appears in the table below.

	Placebo	MEDI-493	total
United States (N=1277)			
RSV hospitalization	44 (10%)	39 (5%)	83 (6%)
no RSV hospitalization	382 (90%)	812 (95%)	1194 (94%)
United Kingdom (N=123)			
RSV hospitalization	4 (10%)	3 (4%)	7 (6%)
no RSV hospitalization	36 (90%)	80 (96%)	116 (94%)
Canada (N=102)			
RSV hospitalization	5 (15%)	6 (9%)	11 (11%)
no RSV hospitalization	29 (85%)	62 (91%)	91 (89%)

Primary Efficacy Endpoint/ by Baseline Diagnosis: In addition, two distinct populations of infants participated in this study: premature infants no more than 6 months old, and infants with a diagnosis of BPD who were no more than 24 months old. (How were patients classified if they met both criteria?) The randomization was not stratified to account for these two populations; however, it was anticipated that the rate of RSV hospitalization and the treatment effect may be quite different for these two populations. In fact, the rate of RSV hospitalizations was higher among infants with BPD, and the treatment effect was not as pronounced. A treatment-by-diagnosis interaction was tested using a Breslow-Day test (StatXact). The resulting p-value of 0.028 (based upon an asymptotic distribution) is evidence that the treatment effect may be different in these two populations. The sponsor computed, using Fisher's Exact Test that there is a statistically significant treatment effect in each of the subpopulations. These calculations were verified in StatXact and reported in the summary below.

	Placebo	MEDI-493	total	Fisher's Exact
Infants with BPD (N=762)				
RSV hospitalization	34 (13%)	39 (8%)	689 (90%)	p=0.038
no RSV hospitalization	232 (87%)	457 (92%)	73 (10%)	
Premature infants (N=740)				
RSV hospitalization	19 (8%)	9 (2%)	712 (96%)	p<0.001
no RSV hospitalization	215 (92%)	497 (98%)	28 (4%)	
Breslow-Day test for homogeneity: ($\chi_2 = 4.86$) p=0.028				

Drug Exposure: Overall, compliance with the study protocol was excellent. Over 90% of patients in each arm received all 5 injections. The number of patients receiving fewer than 5 injections was balanced between arms. In the line listings in volumes 73-74 of scheduled injection visits, it appears that the visits were scheduled in advance, but a patient may not have shown up. For five

MEDI-493 patients "lost to follow-up'
according to the study report (p. 40), all had scheduled visits throughout the study period. A summary of number of injections per patient is displayed in the table below:

	Placebo N=500	MEDI-493 N=1002	total N=1502
number of patients receiving:			
0 injections	3 (< 1%)	1 (< 1%)	4 (< 1%)
1 injection	10 (2 %)	21 (2%)	31 (2%)
2 injections	3 (< 1%)	7 (< 1%)	10 (< 1%)
3 injections	5 (1%)	18 (2%)	23 (1.5%)
4 injections	10 (2%)	30 (3%)	40 (2.5%)
5 injections	469 (94%)	925 (92%)	1394 (93%)

Upon inspection, there appears to be no clear difference in the distributions of injections between the two arms. Indeed, a chi-squared test for the difference in the two distributions yielded a p-value of 0.32. However, an issue remains regarding the effect of drug exposure on outcome. This is, in general, difficult to assess, because unless patients are prospectively randomized to receive only some of injections, one doesn't know if drug exposure is influencing outcome or if outcome is influencing drug exposure. Of the 53 children in the placebo arm hospitalized for RSV, 50/53 (94%) had all five injections, while among the 48 children in the MEDI-493 arm hospitalized for RSV, only 37/48 (77%) completed the five injection course.

While these data might suggest that compliance is independent of outcome in the placebo arm, and increased drug exposure leads to more favorable outcomes, one could also hypothesize that dropping out of the treatment arm is related to the inability to tolerate an active agent and therefore may be associated with and unfavorable outcome. Although there is a notable difference between compliance and outcome in the two arms, it is difficult to know how to interpret it. There is the added complication that among the small percent of children who were "non-compliant" (31 (6%) in the placebo arm and 77 (7%) in the MEDI-493 arm), only four children (3 in the placebo arm and 1 in the MEDI-493 arm) refused all treatment. Most of the children were at least partially compliant, and one would have to consider if these children were experiencing RSV hospitalizations during the time they were compliant. A listing of patients with RSV hospitalization and with fewer than 5 injections appears in the table below.

# of injections	treatment	patient #	study days/RSV hospitalization*	study days/ injection received #
1	placebo		79-83	0
3	placebo		10-20	0, 30, 118
4	placebo		143-150	0, 61, 97, 124
1	MEDI-493		24-38	0
1	MEDI-493		81-88	0
3	MEDI-493		51-68	0, 28, 57
3	MEDI-493		88-119	0, 29, 63
3	MEDI-493		45-49	10, 35, 66
4	MEDI-493		67-103	0, 50, 84, 120
4	MEDI-493		41-43	0, 30, 62, 97
4	MEDI-493		28-34	0, 25, 60, 91
4	MEDI-493		64-68	0, 30, 72, 101
4	MEDI-493		68-87	0, 31, 80, 112
4	MEDI-493		68-87	0, 31, 80, 112

*source: volume 61, data listing 22
source: volumes 73-74, data listing 40

The study days of RSV hospitalization and the days of injection are listed in the last two columns. Of the 11 MEDI-493 patients, four had RSV hospitalizations which started more than 30 days after their last exposure, and three patients had RSV hospitalizations which started between 20 and 30 days of last drug exposure.

Covariate Adjustment: We repeated the sponsor's analyses of the potential effect of other covariates on the primary outcome. Using S-PLUS, we considered the effect of each of five covariates separately (treatment assignment, gender, age at study entry, BPD vs. premature, weight at study entry) on the primary outcome, RSV hospitalization. Except for treatment assignment and BPD vs. premature, none of the covariates was a statistically significant predicotr of the primary outcome. A summary of the analysis appears in the table below.

Covariate	parameter estimate (log odds ratio)	Likelihood ratio statistic	p-value	n	group doing better
treatment assignment	-0.86	16.9	< 0.001	1502	MEDI-493
gender	0.20	0.9	0.34	1502	female
entry age (months)	0.009	0.2	0.65	1502	younger
BPD vs. premature	0.99	20.8	< 0.001	1502	premature

Covariate	parameter estimate (log odds ratio)	Likelihood ratio statistic	p-value	n	group doing better
entry weight -	-0.03	0.5	0.48	1495	heavier

In contrast, the sponsor performed a logistic regression using all the above covariates together in a single additive logistic model. The parameter estimates were similar to the estimates in the above table, and the p-values associated with testing each covariate separately, assuming asymptotic normality, were consistent with what was obtained above. The only small difference in the two analyses was that the parameter estimate for age was positive in this reviewer's analysis and negative in the sponsor's analysis. Neither estimate, however, is significantly different from zero, so the fact that they come out on either side of zero is of little relative importance. It should be stressed, however, that for gender, entry age and entry weight, one should put little faith in the hypotheses that younger, or heavier, or female patients are more likelier to have better outcomes than their counterparts.

As part of a separate analysis, we considered other covariates which are associated with sicker patients and may be predictive of the primary outcome: steroid use within the past six months, ongoing steroid use, prior hospitalization for a lower respiratory tract infection (LRTI), supplemental oxygen in the past 6 months, ongoing oxygen use, and multiple birth. As one can see from the table below, all of these covariates except current steroid use were strongly associated with outcome. However, all of these baseline factors were also strongly associated with having a BPD diagnosis, which is also strongly predictive of response. In order to explore to what extent the baseline factor predicts the outcome independent of the BPD diagnosis, we modeled outcome using logistic regression, and considered the differences between the model with BPD alone versus a model with BPD and one of the baseline covariates listed above. A likelihood ratio test weighs the contribution of other baseline factors over and above the contribution of the BPD diagnosis. In no case did the additional covariate add significantly to the model with BPD alone. (see table below). A closer look at data reveals why this is so. Among the 442 patients who had received steroids in the last 6 months, 437 (99%) were diagnosed with BPD. Of the 636 patients who had received supplemental oxygen in the last 6 months, 629 (99%) were diagnosed with BPD.

Covariate	parameter estimate (log odds ratio)	Likelihood ratio statistic	p-value	n	group doing better
BPD vs. premature	0.99	20.8	< 0.001	1502	premature
steroid use within last 6 months	0.71	11.1	< 0.001	1502	no steroids
ongoing steroid therapy	-0.17	0.2	0.65	1502	ongoing steroids
prior LRTI hospitalization	0.75	7.5	0.006	1502	no prior hospitalization
supplemental O_2 in past 6 months	0.87	17.5	< 0.001	1502	no O_2
ongoing supplemental O_2	0.59	4.8	0.03	1502	no O_2
multiple birth (Y/N)	-0.35	2.3	0.13	1502	multiple birth

Covariate	Δ Likelihood ratio statistic	p-value
BPD + O_2 in last 6 months	0.7	0.40
BPD + steroids in last 6 months	0.6	0.44
BPD + prior LRTI hospitalization	2.4	0.12
BPD + ongoing O_2	0.2	0.65

In this series of analyses, we did not identify covariates that were strong predictors of outcome independent of the BPD diagnosis.

Heterogeneity of Treatment Effect Among Subgroups: Among the baseline factors, age (≤ 6 months vs. > 6 months), weight (≤ 5 kg vs. > 5 kg), gestational age (≤ 32 weeks vs. > 32 weeks), race, country, and gender, only gender was identified as a factor in which treatment effects may differ. In males, the treatment effect was more pronounced, with the incidence of hospitalization ranging from 13% (27/284) in the placebo arm to 4% (25/570) in the treatment arm. In contrast, the incidence of hospitalization in females was 7% (16/216) in the placebo arm and 5% (23/432) in the treatment arm. A Breslow-Day test was performed as an exploratory analysis to test the homogeneity of the treatment effect across the two subgroups. Because this was a retrospective

analysis which was part of numerous exploratory analyses, the suggestive results of the analysis cannot be considered conclusive in the absence of additional data.

Treatment Effect by Study Site: There were 139 participating study sites, the largest of which enrolled 25 patients. In the table below, the incidence of hospitalization in every study site enrolling more than 17 patients is tabulated in order by size. These 15 sites accounted for approximately 20% of the total study participants. In these sites, there were ten cases of RSV hospitalization in the placebo arm, accounting for about 20% of all the RSV hospitalizations observed in the placebo arm. In the MEDI-493 arm, there were only 6 observed cases of RSV hospitalization, accounting for only 12.5% of the total observed cases in the MEDI-493 arm. The study sites in which the MEDI-493 arm had a higher rate of RSV hospitalization are highlighted. As one may notice, the differences in the incidence of RSV hospitalizations in these larger centers between treatment groups is fairly consistent with what one sees in the overall study.

Study Site	MEDI-493 RSV/total	Placebo RSV/total	all patients RSV/total
053	0/16	0/9	0/25
090	0/15	0/8	0/23
239	0/14	0/7	0/21
227	0/14	1/7	1/21
073	1/14	2/7	3/21
274	0/13	3/7	3/20
187	0/14	0/6	0/20
136	1/13	1/7	2/20
273	**1/13**	**0/6**	**1/19**
179	1/12	1/7	2/19
207	0/12	0/6	0/18
109	0/12	0/6	0/18
072	0/12	1/6	1/18
050	2/12	1/6	3/18
038	0/12	0/6	0/18
total	*6/198*	*10/101*	*16/299*

Sites with Increased Risk: The electronic data did not provide the study region with the study site numbers. Only the country code was available. It was anticipated that there may be a strong regional effect with respect to the overall incidence of RSV infection. For this reason, we attempted to pinpoint individual study sites which had an unusually higher overall incidence of RSV hospitalizations. Any site with at least 4 cases of RSV hospitalization or 3 cases and an overall incidence rate of at least 0.20 were included. In addition, any site with at least 2 cases of

RSV hospitalization and an incidence rate of at least 0.20 in either one of the arms was also included. Ten sites met the above criteria, accounting for approximately 10% of the study participants and 35% of the total number of observed RSV hospitalizations. The RSV hospitalizations for these sites are summarized in the table below. As in the above table, the study sites with a higher incidence of RSV hospitalization in the MEDI-493 arm are highlighted.

Study Site	MEDI-493 RSV/total	Placebo RSV/total	all patients RSV/total
073	1/14	2/7	3/21 (14%)
274	0/13	3/7	3/20 (15%)
142	2/10	3/5	5/15 (33%)
231	**4/10**	**1/5**	**5/15 (33%)**
110	**2/10**	**0/5**	**2/15 (13%)**
037	2/8	1 /4	3/12 (25%)
205	1/8	2/4	3/12 (25%)
214	**2/8**	**0/4**	**2/12 (17%)**
188	1/7	3/4	4/11 (36%)
224	1/5	2/2	3/7 (43%)
152	**2/4**	**0/2**	**2/6 (33%)**
total	*18/97 (19%)*	*17/49 (35%)*	*35/146 (24%)*

In these centers, the RSV hospitalization rate was about twice as high in the placebo arm as in the MEDI-493 arm, consistent with the treatment effect seen in the overall study. The odds ratio estimating the treatment effect in the overall study was 0.42; in this "high incidence" subset, the odds ratio was 0.43.

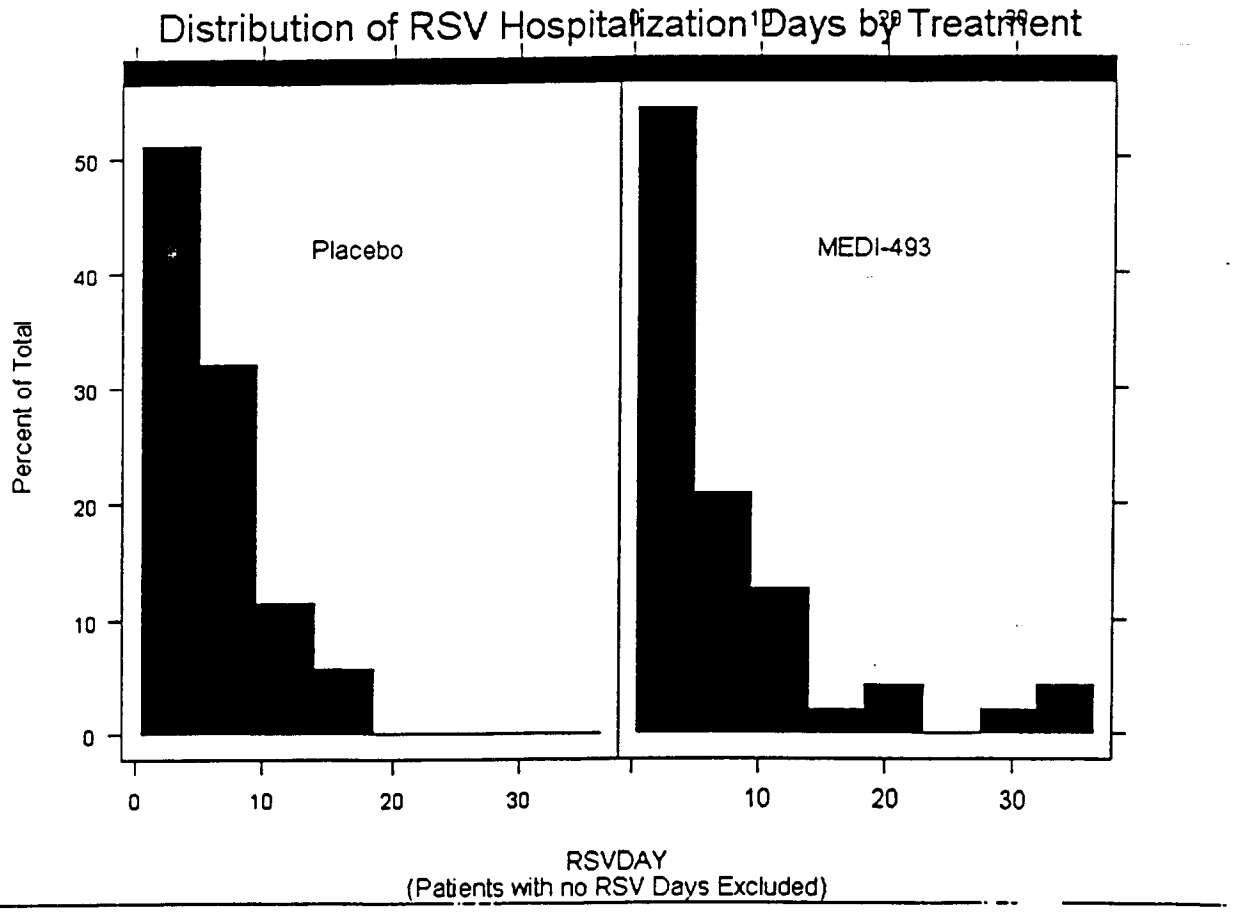
SECONDARY ENDPOINTS/ FDA ANALYSES

Incidence of other "Bad" Outcomes: Death, mechanical ventilation, ICU admission, supplemental oxygen requirements were other endpoints in this study. Rather than looking at each of them separately, we considered them together as parts of a spectrum of events which occurred in the study. The events were ordered by severity of outcome, the worst outcome being death, followed by mechanical ventilation, ICU admission, supplemental oxygen required, RSV hospitalization or none of the above. Each patient was classified according their worst outcome category. With the exception of death, all patients who fell into a "bad" outcome category (e.g. mechanical ventilation) experienced all of the "less bad" alternatives (ICU admission, supplemental oxygen, and RSV hospitalization). Of the nine patients who died on study (5 in the placebo arm and 4 in the MEDI-493 arm), only two patients, both in the MEDI-493 arm, died of RSV complications. None of the other seven patients were hospitalized for RSV infection. A summary of these data appear in the table below.

treatment	Dead	required mechanical ventilation	admitted to ICU	required supplementary O_2	RSV hosp.	No RSV hosp.	
MEDI-493	4 (0.4%)	5 (0.5%)	6 (0.6%)	20 (2%)	15 (1.5%)	952 (95%)	**1002 (100%)**
placebo	5 (1%)	1 (0.2%)	14 (2.8%)	25 (5%)	13 (2.6%)	442 (88%)	**500 (100%)**
total	**9 (0.6%)**	**6 (0.4%)**	**20 (1.3%)**	**45 (3%)**	**28 (1.9%)**	**1394 (93%)**	**1502**

Using StatXact, an exact Komolgorov-Smirnov test was used to test equality of the two distributions. The evidence that the group treated with MEDI-493 had better outcomes (stochastically larger) was very strong, with a p-value less than 0.0001. From inspection, one can see that the proportion of patients with "bad-to-worse" outcomes was consistently higher in the placebo-treated arm.

Number of Days of RSV Hospitalization: The total number of RSV hospitalization days was compared between groups by this reviewer using both a Wilcoxon Rank Sum Test and a two sample t-test. In the study report submitted by the sponsor, Wilcoxon Rank-Sum tests were done, and the reported p-values were less than 0.001, favoring the treatment arm. The Wilcoxon Rank-Sum test ($p < 0.001$) and the t-test ($p=0.04$) offer different interpretations of the strength of the evidence of a treatment effect, although both support that a treatment effect is present. At issue are a handful of patients in the MEDI-493 arm with unusually long RSV hospital stays. The data from these patients had a large influence on the sample mean (0.36 days in the treatment arm and 0.63 days in the control arm), and consequently on the p-value of the two-sample t-test. In contrast, the Wilcoxon Rank-sum Test does not take into account the actual number of hospital days, but only the ranking of that number relative to the other data. The histogram below shows the distribution of the number of RSV hospitalization days, excluding those patients with no RSV hospitalizations. These patients were excluded because they represented close to 90% of the study participants and in their presence, differences within the smaller group were not easily seen.



A total of seven patients were hospitalized for RSV infection for at least 15 days. Six of these patients (0.6%) were in the MEDI-493 arm and two (0.4%) were in the placebo arm. Hospitalization information on these patients is included in the table below:

patient #	treatment	#RSV days	# ICU days	# days mech. vent.	# days supp. O_2	# days any hospitalization
	placebo	18	18	0	19	18
	placebo	15	7	0	13	37
	MEDI-493	35	30	19	37	64
	MEDI-493	36	28	17	26	38
	MEDI-493	17	15	10	15	24
	MEDI-493	31	21	19	27	34
	MEDI-493	19	3	0	17	19
	MEDI-493	19	0	0	17	43

Other Hospital Day Endpoints: Total hospital days with increased oxygen requirements, total hospital days with LRI score of at least 3, total days of ICU, and total hospital days for any cause were compared between the two groups using both a Wilcoxon Rank Sum Test and a two-sample t-test. As in the analysis of total days of RSV hospitalization, a small handful of patients in the

MEDI-493 arm (the same patients) were hospitalized for extended periods, so the sample mean and the t-test were heavily influenced by these few patients. Summary statistics for these endpoints are displayed in the table below:

endpoint	MEDI-493 (N=1002) sample mean (range)	Placebo (N=500) sample mean (range)	p-value
Hosp. Days of Increased O_2	0.30 (0-32)	0.51 (0-19)	t-test p=0.08 Wilcoxon p<0.001
Hosp. Days LRI ≥ 3	0.30 (0-37)	0.47 (0-16)	t-test p=0.13 Wilcoxon p<0.001
Days in ICU	0.13 (0-37)	0.13 (0-16)	t-test p=0.94 Wilcoxon p=0.02
Total Hospital Days	1.91 (0-81)	2.42 (0-123)	t-test p=0.21 Wilcoxon p=0.005

We also considered the number of times patients were hospitalized for different causes. For this exploratory analysis, we counted all line listings from the SAS data set "Hosparm", and classified each listing by type of hospitalization and treatment assignment. However, a patient with any extended hospitalization stay during which time he was admitted or discharged from the ICU a couple of times would have multiple line listing for this single visit. This was the case for at least one patier ——— in the MEDI-493 arm. Because this was an exploratory analysis and there were unlikely to be more than a handful of such cases, we counted each line listing as a separate visit. The results of this tabulation appear below.

Treatment	Type of Hospitalization non-respiratory	respiratory	RSV	total
Placebo	72	103	54	229
MEDI-493	143	182	52	377

Since the randomization was 2:1 treatment-to-placebo, one would expect that for an endpoint not related to treatment, the number of events observed in the MEDI-493 arm would be approximately twice the number of events observed in the placebo arm. This appears to be the case for each of the non-RSV hospitalizations. However, for RSV hospitalizations, the number of events in the MEDI-493 arm is less than half that what one would expect when the treatment is unrelated to outcome.

CONCLUSIONS

This application supports the licensure of MEDI-493 for the prophylaxis of severe RSV in premature infants under 6 months old and infants with BPD under 2 years old.

COVARIATE ANALYSIS OF PRIMARY ENDPOINT: RSV HOSPITALIZATION (S-PLUS)

```
> summary(glm(RSV~TMTNO, family=binomial, data=rieves1) )

Call: glm(formula = RSV ~ TMTNO, family = binomial, data = rieves1)
Deviance Residuals:
     Min       1Q   Median       3Q      Max
-0.473391 -0.473391 -0.3133359 -0.3133359 2.465178

Coefficients:
             Value Std. Error   t value
(Intercept) -1.2750724  0.3259801 -3.911504
     TMTNO -0.8571943  0.2072392 -4.136255

(Dispersion Parameter for Binomial family taken to be 1 )

    Null Deviance: 740.3362 on 1501 degrees of freedom

Residual Deviance: 723.4338 on 1500 degrees of freedom

Number of Fisher Scoring Iterations: 5

Correlation of Coefficients:
     (Intercept)
TMTNO -0.9481497
> summary(glm(RSV~SEX, family=binomial, data=rieves1))

Call: glm(formula = RSV ~ SEX, family = binomial, data = rieves1)
Deviance Residuals:
     Min       1Q   Median       3Q      Max
-0.3882789 -0.3882789 -0.3882789 -0.3524314 2.370585

Coefficients:
             Value Std. Error    t value
(Intercept) -2.647508  0.1043847 -25.3629886
      SEX  0.100225  0.1043847   0.9601506

(Dispersion Parameter for Binomial family taken to be 1 )

    Null Deviance: 740.3362 on 1501 degrees of freedom

Residual Deviance: 739.4225 on 1500 degrees of freedom

Number of Fisher Scoring Iterations: 4

Correlation of Coefficients:
    (Intercept)
SEX -0.2143798
> summary(glm(RSV~AGE, family=binomial, data=rieves1))

Call: glm(formula = RSV ~ AGE, family = binomial, data = rieves1)
Deviance Residuals:
     Min       1Q   Median       3Q      Max
-0.4048242 -0.3742126 -0.3702411 -0.3672192 2.34461

Coefficients:
             Value Std. Error    t value
(Intercept) -2.683926082 0.16128832 -16.6405488
      AGE  0.009289998 0.02107481   0.4408105

(Dispersion Parameter for Binomial family taken to be 1 )

    Null Deviance: 740.3362 on 1501 degrees of freedom
```

```
Residual Deviance: 740.1485 on 1500 degrees of freedom

Number of Fisher Scoring Iterations: 4

Correlation of Coefficients:
   (Intercept)
AGE -0.774845
> summary(glm(RSV~ENSTATUS, family=binomial, data=rieves1))

Call: glm(formula = RSV ~ ENSTATUS, family = binomial, data = rieves1)
Deviance Residuals:
     Min       1Q   Median       3Q      Max
-0.4487879 -0.4487879 -0.2777513 -0.2777513 2.559074

Coefficients:
             Value Std. Error   t value
(Intercept) -2.7403194  0.1140888 -24.019181
  ENSTATUS -0.4955376  0.1140888  -4.343438

(Dispersion Parameter for Binomial family taken to be 1 )

    Null Deviance: 740.3362 on 1501 degrees of freedom

Residual Deviance: 719.5089 on 1500 degrees of freedom

Number of Fisher Scoring Iterations: 5

Correlation of Coefficients:
      (Intercept)
ENSTATUS 0.4180413
> summary(glm(RSV~WEIGHT, family=binomial, data=rieves1))
Error in function(object, ...): missing values not allowed: found in WEIGHT
Dumped
> summary(glm(RSV~WEIGHT, family=binomial,na.action=na.omit, data=rieves1))

Call: glm(formula = RSV ~ WEIGHT, family = binomial, data = rieves1, na.action = na.omit)
Deviance Residuals:
     Min       1Q   Median       3Q      Max
-0.3966142 -0.3832815 -0.3743839 -0.36321 2.383709

Coefficients:
             Value Std. Error   t value
(Intercept) -2.46546863 0.24541811 -10.0459931
   WEIGHT -0.03334322 0.04735209  -0.7041553

(Dispersion Parameter for Binomial family taken to be 1 )

    Null Deviance: 739.3592 on 1494 degrees of freedom

Residual Deviance: 738.8651 on 1493 degrees of freedom

Number of Fisher Scoring Iterations: 4

Correlation of Coefficients:
     (Intercept)
WEIGHT -0.9095531

>
```

```
> wilcox.test(rieves1$SUPO2[rieves1$TMTNO==0], rieves1$SUPO2[rieves1$TMTNO==1])

        Wilcoxon rank-sum test

data:  rieves1$SUPO2[rieves1$TMTNO == 0] and rieves1$SUPO2[rieves1$TMTNO == 1]
rank-sum normal statistic with correction Z = 3.9356, p-value = 0.0001
alternative hypothesis: true mu is not equal to 0

Warning messages:
1: cannot compute exact p-value for n larger than 50 in: wil.rank.sum(x, y, alternative, exact, correct)
2: cannot compute exact p-value with ties in: wil.rank.sum(x, y, alternative, exact, correct)
> wilcox.test(rieves1$LRIGE3[rieves1$TMTNO==0], rieves1$LRIGE3[rieves1$TMTNO==1])

        Wilcoxon rank-sum test

data:  rieves1$LRIGE3[rieves1$TMTNO == 0] and rieves1$LRIGE3[rieves1$TMTNO == 1]
rank-sum normal statistic with correction Z = 4.2192, p-value = 0
alternative hypothesis: true mu is not equal to 0

Warning messages:
1: cannot compute exact p-value for n larger than 50 in: wil.rank.sum(x, y, alternative, exact, correct)
2: cannot compute exact p-value with ties in: wil.rank.sum(x, y, alternative, exact, correct)
> wilcox.test(rieves1$ICUDAY[rieves1$TMTNO==0], rieves1$ICUDAY[rieves1$TMTNO==1])

        Wilcoxon rank-sum test

data:  rieves1$ICUDAY[rieves1$TMTNO == 0] and rieves1$ICUDAY[rieves1$TMTNO == 1]
rank-sum normal statistic with correction Z = 2.2504, p-value = 0.0244
alternative hypothesis: true mu is not equal to 0

Warning messages:
1: cannot compute exact p-value for n larger than 50 in: wil.rank.sum(x, y, alternative, exact, correct)
2: cannot compute exact p-value with ties in: wil.rank.sum(x, y, alternative, exact, correct)
> wilcox.test(rieves1$ANYDAYS[rieves1$TMTNO==0], rieves1$ANYDAYS[rieves1$TMTNO==1])

        Wilcoxon rank-sum test

data:  rieves1$ANYDAYS[rieves1$TMTNO == 0] and rieves1$ANYDAYS[rieves1$TMTNO == 1]
rank-sum normal statistic with correction Z = 2.8234, p-value = 0.0048
alternative hypothesis: true mu is not equal to 0

Warning messages:
1: cannot compute exact p-value for n larger than 50 in: wil.rank.sum(x, y, alternative, exact, correct)
2: cannot compute exact p-value with ties in: wil.rank.sum(x, y, alternative, exact, correct)
> t.test(rieves1$SUPO2[rieves1$TMTNO==0], rieves1$SUPO2[rieves1$TMTNO==1])

        Standard Two-Sample t-Test

data:  rieves1$SUPO2[rieves1$TMTNO == 0] and rieves1$SUPO2[rieves1$TMTNO == 1]
```

```
t = 1.7284, df = 1500, p-value = 0.0841
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.02732426  0.43253783
sample estimates:
 mean of x mean of y
    0.506 0.3033932

> t.test(rieves1$LRIGE3[rieves1$TMTNO==0], rieves1$LRIGE3[rieves1$TMTNO==1])

        Standard Two-Sample t-Test

data:  rieves1$LRIGE3[rieves1$TMTNO == 0] and rieves1$LRIGE3[rieves1$TMTNO == 1]
t = 1.5147, df = 1500, p-value = 0.1301
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.05238636  0.40757199
sample estimates:
 mean of x mean of y
    0.474 0.2964072

> t.test(rieves1$ICUDAY[rieves1$TMTNO==0], rieves1$ICUDAY[rieves1$TMTNO==1])

        Standard Two-Sample t-Test

data:  rieves1$ICUDAY[rieves1$TMTNO == 0] and rieves1$ICUDAY[rieves1$TMTNO == 1]
t = -0.0779, df = 1500, p-value = 0.9379
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.1634280  0.1509455
sample estimates:
 mean of x mean of y
 0.1270984 0.1333397

> t.test(rieves1$ANYDAYS[rieves1$TMTNO==0], rieves1$ANYDAYS[rieves1$TMTNO==1])

        Standard Two-Sample t-Test

data:  rieves1$ANYDAYS[rieves1$TMTNO == 0] and rieves1$ANYDAYS[rieves1$TMTNO == 1]
t = 1.2607, df = 1500, p-value = 0.2076
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.2836196  1.3039161
sample estimates:
 mean of x mean of y
  2.421768   1.91162

>
```

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE June 2, 1998

FROM Mary Andrich, Bioresearch Monitoring, HFM-650
Division of Inspections and Surveillance, Office of Compliance
Telephone: 301-827-6221 FAX: 301-443-3874

TO Dr. Robert Anderson
Chair, BLA Committee

SUBJECT Bioresearch Monitoring Inspection Results
BLA 97-1359
Product: MEDI-493 (Palivizumab)
Sponsor: MedImmune, Inc.

STUDY TITLE

A Pivotal Phase III Study of MEDI-493, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, for the Prophylaxis of Severe RSV Disease in Premature Infants and Infants with Bronchopulmonary Dysplasia (BPD); Protocol MI-CP018

SUMMARY STATEMENT

The results of bioresearch monitoring inspections of three clinical sites indicate that the deviations made by the clinical investigators are not substantive, with the exceptions noted, and that the submitted data can be considered reliable and accurate.

BACKGROUND

Inspections of three clinical investigators were performed in support of the subject BLA. The inspections were conducted in accordance with FDA's Compliance Guidance Manual. The inspections focused on subjects enrolled in Protocol Number MI-CP018, and included specific questions concerning the study. Data audits were performed at three clinical trial sites:

Site	P.I.	FDA Form 483	Classification
Spokane, WA	Stephen R. Luber	Yes	NAI
Houston, TX	Leonard Weisman	No	NAI
Pittsburgh, PA	Donald M. Null, Jr.	No	NAI